IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	: Attorney Docket No. 2006_1477A
Shinichi HIROSE et al.	: **Confirmation No. 3395**
Serial No. 10/591,587	: Group Art Unit 1633
Filed October 23, 2006	: Examiner HIRIYANNA, KELAGINAMANET
ELILEPSY MODEL ANIMAL (CHRNA4:S284L)	: **Mail Stop: AMENDMENT**

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
Washington, D.C.

Sir:

I, Tatsuya TANAKA, the undersigned, do hereby declare:

1. That I am Honorary Director, Yamabiko Medical Welfare Center, 1779, Minayoshi-cho, Kagoshima 891-1206 Japan.

2. That my EDUCATIONS, EXPERIENCES, AWARDS and ADDITIONAL SERVICES are in the attached "CURRICULUM VITAE".

3. That I have published literatures and books as listed in the attached "PUBLICATIONS".

4. As shown above, I am a brain surgeon and have been engaged in surgical treatment of intractable epilepsy, as well as in basic research with animal models including a kainic acid-induced epilepsy model and a kindling animal model. Further, I am well familiar with the epilepsy arts since I was the president of The Japan Epilepsy Society and am now the first vice-president of The International League Against Epilepsy (ILAE).

With regard to Advisory Action in connection with the above-identified application dated July 9, 2010, it is my expert opinion and belief that it is difficult for the skilled artisan to anticipate that the claimed transgenic rat (CHRNA4:S284L) expresses a phenotype similar to

human chromosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), i.e., spontaneous epileptic seizures during sleep (nocturnal paroxysmal arousal). It is very difficult to induce epileptic seizures in rats compared to mice. In fact, almost all animal epilepsy models having genetic modifications are established using mice.

Regarding to the mutated CHRNA4 or CHRNB2 in connection with ADNFLE, genetically modified mice are proposed as a model animal (References 1-9 attached). Almost all of those mice have drug "induced" epileptic seizures (ex. pentylenetetrazol). While only three lines (references 6, 8 9) have spontaneous epileptic seizure, these mice don't express the phenotype of human ADNFLE, spontaneous epileptic seizure during sleep.

Reference

1. Picciotto MR, Zoli M, Rimondini R et al. Acetylcholine receptors containing the β2 subunit are involved in the reinforcing properties of nicotine. Nature. 391, 173-177 (1998).
2. Marubio LM, del Mar Arroyo-Jimenez M et al. Reduced antinociception in mice lacking neuronal nicotinic receptor subunits. Nature. 398, 805-810 (1999).
3. Ross SA, Wong JY, Clifford JJ et al. Phenotypic characterization of an α4 neuronal nicotinic acetylcholine receptor subunit knock-out mouse. J. Neurosci. 20, 6431-6441 (2000).
4. Cohen G, Han ZY, Grailhe R et al. β2 nicotinic acetylcholine receptor subunit modulates protective responses to stress: A receptor basis for sleep-disordered breathing after nicotine exposure. Proc. Natl. Acad. Sci. U. S. A. 99, 13272-13277 (2002).
5. Wong JY, Ross SA, McColl C et al. Proconvulsant-i 580 nduced seizures in α4 nicotinic acetylcholine receptor subunit knockout mice. Neuropharmacology. 43, 55-64 (2002).
6. McColl CD, Horne MK, Finkelstein DI, Wong JY, Berkovic SF, Drago J. Electro585 encephalographic characterisation of pentylenetetrazole-induced seizures in mice lacking the α4 subunit of the neuronal nicotinic receptor. Neuropharmacology. 44, 234-243 (2003).
7. Klaassen A, Glykys J, Maguire J, Labarca C, Mody I, Boulter J. Seizures and enhanced cortical GABAergic inhibition in two mouse models of human autosomal dominant nocturnal frontal lobe epilepsy Proc. Natl. Acad. Sci. U. S. A. 103, 19152-19157 (2006).

8. Teper Y, Whyte D, Cahir E et al. Nicotine-induced dystonic arousal complex in a mouse line harboring a human autosomal-dominant nocturnal frontal lobe epilepsy mutation. J. Neurosci. 27, 10128-10142 (2007).
9. Manfredi I, Zani AD, Rampoldi L et al. Expression of mutant β2 nicotinic receptors during development is crucial for epileptogenesis. Hum. Mol. Genet. 18, 1075-1088 (2009).

Thus, based on the above knowledge in the art and my expert opinion and belief, it is surprising and unexpected that the claimed transgenic rat (CHRNA4:S284L) of this application has the phenotype of human ADNFLE. It is also my expert opinion and belief that such animal model is important and useful for epileptic seizure research for humans.

I further declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Date: October 5, 2010

(Signature of Declarant)